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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,271	09/09/2004	Kristof Van Emelen	PRD 2025-PCT	4912

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,271	VAN EMELEN ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 1-7 and10-12, drawn to compound of formula I, wherein Q=C, X=N, Y=N, namely pyrimidine, process of making, pharmaceutical composition and method of use, in the reply filed on 5/15/2007 is acknowledged.

The traversal is on the ground(s) that examiner's assessment that Groups I-VI are "not so linked as to form a single general inventive concept under PCT Rule 13.1" lacks the required support. This not correct for reasons of record. To repeat:

Where there is lack of unity the requirement for restriction is proper- See MPEP 803.02. The requirement for unity of invention is two-fold: (1) common utility and (2) sharing a substantial structural feature disclosed as being essential to the utility.

Invention I, II, III, IV, V and IV are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core, namely, 1,2,4-triazine versus pyridazine versus pyrimidine, versus pyrazine versus isomeric pyridine and other heterocyclic cores depending upon the choice of the side chain. They can be made and used independently. Art which may render obvious or anticipate one of the groups would not necessarily do the same for the other group. For example prior art cited in the International Search Report may not be applicable to all the above groups. Each can support a patent as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group.

Except for the CO-N group and ring nitrogen, every element and core is varied and it cannot be said that the said group and core essentially contributes to utility recited in the claims. Thus the common structural feature essential for the said utility is not met with.

In addition, common utility requirement is also not met with as evident form the claims that these compounds can be used for treating cancer, fibrosis and as antibacterial agent, antifungal agents etc. Thus, both the criteria set forth for unity of invention is not met with.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Thus, it is clear that the instant invention does not meet both the criteria set forth for unity of invention and applicants have not provide any evidence show that each of the invention is not patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-7 and 10-12 will be examined to the extent they embrace the elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

References cited in the Information Disclosure Statement filed on 9/9/2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1, Recitation of " the N-oxide forms, the pharmaceutically acceptable salts and the stereo-chemically isomeric forms thereof" in claim 1 renders claim 1 and its dependent claims 2-7 and 10-12 indefinite for more than one reason. First of the term "the" lacks antecedent basis. Recitation of Markush choices in plural and use of the conjunction "and" renders claim 1 unclear as to whether the claim is a compound claim or a composition of mixture of the above said Markush choices. Note Markush choices should be in singular and in alternate form. Replacement of " the N-oxide forms, the pharmaceutically acceptable salts and the stereo-chemically isomeric forms thereof' with " N-oxide form, the pharmaceutically acceptable salt or stereo-chemically isomeric forms thereof" is suggested.

2. Recitation of "another zinc chelating group" in claim 1 and claim 2 renders claims 1, 2 and its dependent claims 3-7 and 10-12 indefinite as it is not clear what this group is and what is intended by "another".

3. Regarding claim 10, the phrase "such as for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

4. Claim 10 recites: "A process for the preparing a compound as claimed in claim 1, however, the reaction scheme depicted in the claim is not directed towards the preparation of a compound of formula (I), but it is drawn to a process of preparation of compounds of formula (I-a) wherein R1 is -C(O)NHOH.

5. Claim 11 is vague and unclear. First of it is not clear what is meant by HDAC, Secondly, the preamble recites "detecting" and the process also recites detecting. It is not clear. The claim also recites labeled compound as defined in claim 1. But claim 1 has no labeled compound.

6. Claim 12 has "an" before anticancer agents. The claim is also vague and unclear as it recites HDAC inhibitor as claimed in claim 1. But claim 1 does not have such an attribute.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) wherein R^1 is -C(O)NR^7R^8, -N(H)C(O)R^9, - C(O)-C_{1-6} alkanediylSR^9, -NR^{10}C(O)N(OH)R^9, -NR^{10}C(O)C_{1-6} alkanediylSR^9, and - NRSC(O)C=N(OH)R^9, does not reasonably provide enablement for a compound of formula (I) wherein R^1 is 'another Zn-chelating-group'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The specification fails to enable the preparation of the entire scope of the claimed compounds. The general synthesis route disclosed at pages 15-16 in the specification provides the essential starting materials to prepare the claimed compounds of formula (I) wherein R^1 is a specific group, however, there is no disclosure of the sources of starting materials needed to prepare for compounds wherein R^1 is any other type of Zn-chelating-group. As can be seen from the process claim 10, which provides a process for the preparation of the compounds wherein R^1 is -C(O)NHOH and does not include the preparation of the compounds for any other types of groups recited under R^1. The specification exemplifies processes of preparing the compounds wherein R^1 is as defined by the terms -C(O)NH(OH) and -NH-C(O)-CH2-SH, however, does not provide any explanation or sources such that a person of ordinary skill could determine if a particular group is suitable to be a "Zn-chelating-group" for the claimed structural formula.

In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples and the general unpredictability of chemical

reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. The starting material sources necessary to obtain the instant compounds must have been available as of the filing date in order to provide an enabling disclosure. See In re Howarth, 654 F.2d 103,210 USPQ 689 (CCPA 1981); Exparte Moersch, 104 USPQ 122 (POBA 1954). Applicants should show that the sources of these starting materials was common knowledge or readily available at the time of filing.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating ovarian carcinoma; and a pharmaceutical composition comprising the compound of formula (I) and pharmaceutically acceptable carrier, does not reasonably provide enablement for a method of treating proliferative diseases generally; a method of detecting or identifying a histone deacetylase in a biological sample; and a combination of all types of anti-cancer agents and the compound of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. "In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Exparte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and

use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 11 is drawn to 'a method of detecting and identifying a histone deacetylase (HDAC)' with intended use to 'a method of treating proliferative disease'. The instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The specification defines the term 'biological sample' at page 19, lines 30-31 as 'body tissue or body fluids'. The broadest interpretation of the term '.'biological sample", without limitation reads on many and all types of biological samples, which can include mammals or animals and therefore, the claimed method is seen to encompass an inhibitory method wherein the compound is administered to an animal. This is further evident from the purpose of the inhibition activity of histone deacetylase stated in page 17-19, which includes for example, treatment of a variety of diseases. As the inhibition activity is seen to be useful for the treatment of a variety of diseases, the instant claim implicitly reads on the inherent therapeutic methods characterized by the activity, which as per the specification includes numerous types of disorders.

The instant claim 12 is drawn to 'a combination of anti-cancer agents and a HDAC inhibitor of claim 1 and the specification does not provide sufficient written description regarding such combination compositions. The specification on pages 21-23

provides various anti-cancer agents as examples 'anti-cancer agents' intended by the instant claims, however, the scope of the claims includes agents that are known and those that may be discovered in future, for which there is no enablement. Specifically, the examples in the specification include generic groups or agents such as platinum coordination compounds, taxane compounds, topoisomerase inhibitors etc. all of which include numerous species and there is insufficient guidance in the specification to enable one of ordinary skill in the art how the compounds of the invention and the other biological agent provide a synergistic activity to achieve the desired results.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. Regarding HDAC inhibitors, Glaser (Biochemical Pharmacology 2007) reports that "the full potential of these inhibitors (epigenetic modulators) is still on the horizon, as the true breadth of their utility as anti-cancer agents will be determined by the careful analysis of gene expression changes generated by these inhibitors and then combined with conventional

chemotherapy to synergistically improve response and toxicity for an overall enhanced therapeutic benefit to the patient" (see the abstract). This is clearly indicative of the fact that the therapeutic role of these types of inhibitors is very speculative.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571)

272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

7/22/2007